Transmissible Spongiform Encephalopathies (TSEs): BSE, CJD, vCJD & the Blood Supply

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CBER Concern: Prevent Transmission of TSE (Prion) Infections via Regulated Products

- **Human TSEs: Creutzfeldt-Jakob Disease (CJD), variant CJD (vCJD)** and others less common (kuru, GSS, FFI, SFI)
  - **Iatrogenic transmission**
    - Vaccines: theoretical risk for humans
    - **Blood and blood products: theoretical risk**
    - Other human cellular and tissue-based products: demonstrated risk for cornea, dura mater
- **Animal TSEs**
  - **Bovine spongiform encephalopathy (BSE)**
    - potential importation/amplification of BSE in USA
    - potential transmission to humans of BSE agent in USA
  - Other animal TSEs (scrapie, CWD, etc.)
    - potential transmission to humans (and animals)

TSEs and Safety of the Blood Supply

- Iatrogenic TSEs and FDA concerns
- BSE and the new “variant” CJD
- Control of BSE: protecting human health
- Theoretical risk of TSE agents in human blood
- CBER Guidance to reduce TSE blood risk
- Plasma derivatives: lower risk than components
- Steps to prevent exposure to BSE agent in food
- Miscellaneous comments: tissue risk, recent events in research and public health, CBER TSE research efforts, CBER staff credits
- Regulatory action and control of TSEs: a lesson from the past

Evaluating Risk of Accidental Transmission of a Spongiform Encephalopathy: People Potentially Exposed to TSE Agent†

(WHO: www.who.int/emc-documents/tse/docs/whocdscsraph20003.pdf)

- **Recipients of potentially contaminated products (demonstrated risk)**
- Other patients in medical, dental facilities
- Health-care workers
  - Medical, dental care providers
  - diagnostic-laboratory staff
- Autopsy and mortuary staff
- Contacts: family, friends (negligible risk)

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† decreasing order of concern

Transmissible Spongiform Encephalopathies: Past FDA Regulatory Activities (partial)

- Regulation: June 1997 … Animal Proteins Prohibited in Ruminant Feed; Final Rule ("Feed Ban")
- Guidance letters to manufacturers requesting information about and use of BSE-free ruminant materials (from 1991)
  - 1993 & seq: Requests to use BSE-free bovine materials in FDA-regulated products
  - 1997: Guidance on bovine gelatin
- **Guidance letters &c concerning CJD (from 1987)**
  - **1987 & seq: Risk reduction for blood products (CBER)**
  - **1990, rev 1999: Processed dura mater allograft (CDRH)**

Iatrogenic Transmission of CJD by Products of Human Origin

Product	# Pts	Incubation Mean	Range
Cornea	2 (?3)	17 mo	6, 18 mo
Dura mater	?110	7.4 yr	1.3 to 16 yr
Pit. hormones			
• growth	?130*	12 yr	5 to 39 yr
• gonadotropin	4	13 yr	12 to 16 yr

* 23/~8000 recipients in USA

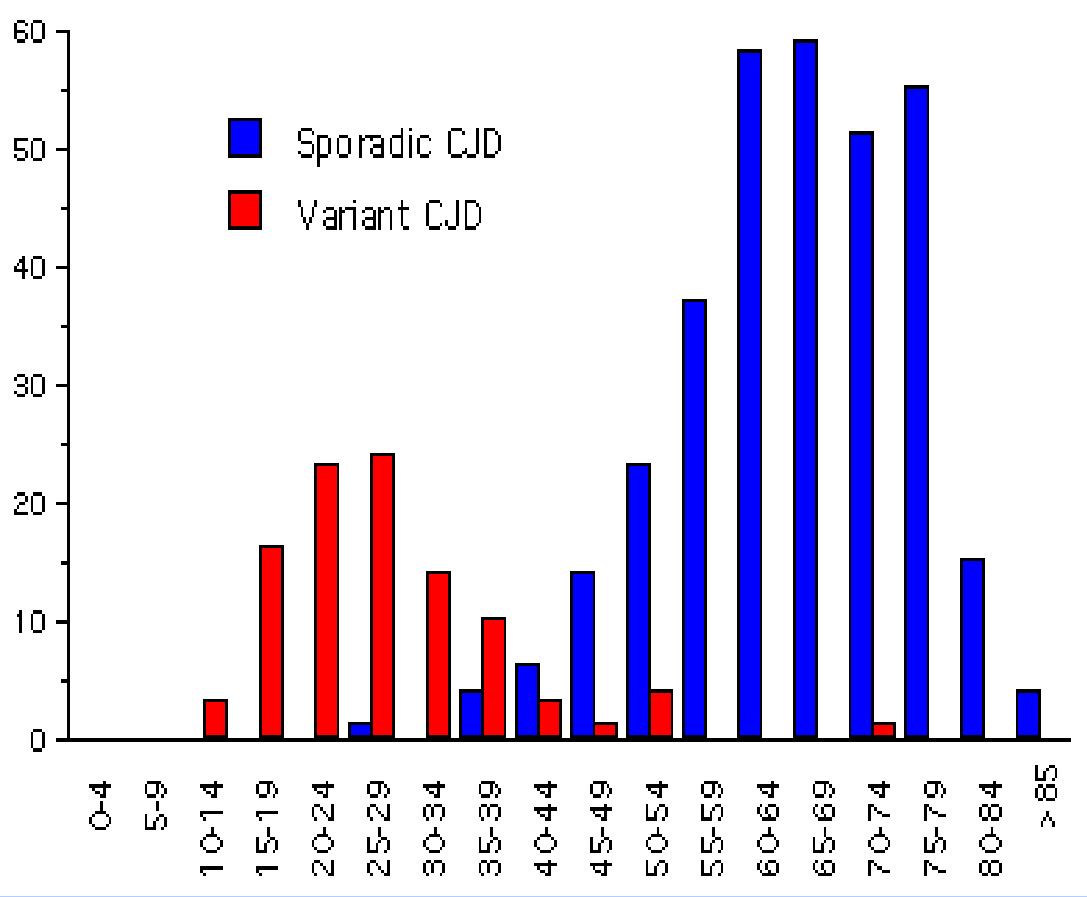
138 Cases of Probable or Confirmed Variant CJD (vCJD) in Seven Countries

[Sept 2002]

UK - 127
France - 6
Hong Kong – 1*
Ireland – 1*
Italy - 1
US – 1*
Canada – 1*

*** Long-time UK residents**

Age Distribution of CJD in UK
CJD and vCJD 1994-2001
(Taffs R & al. FDA Science Forum 2002)

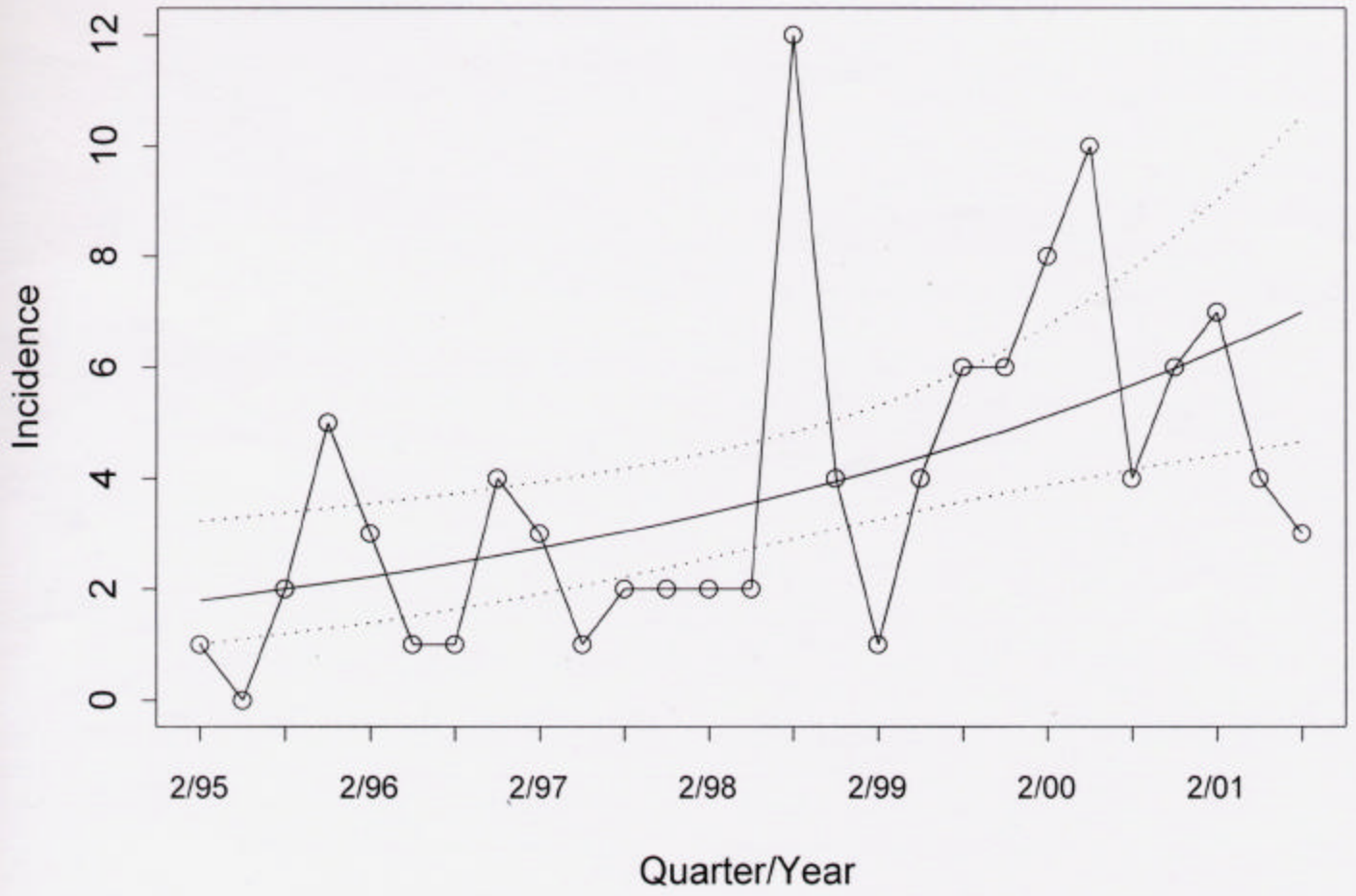


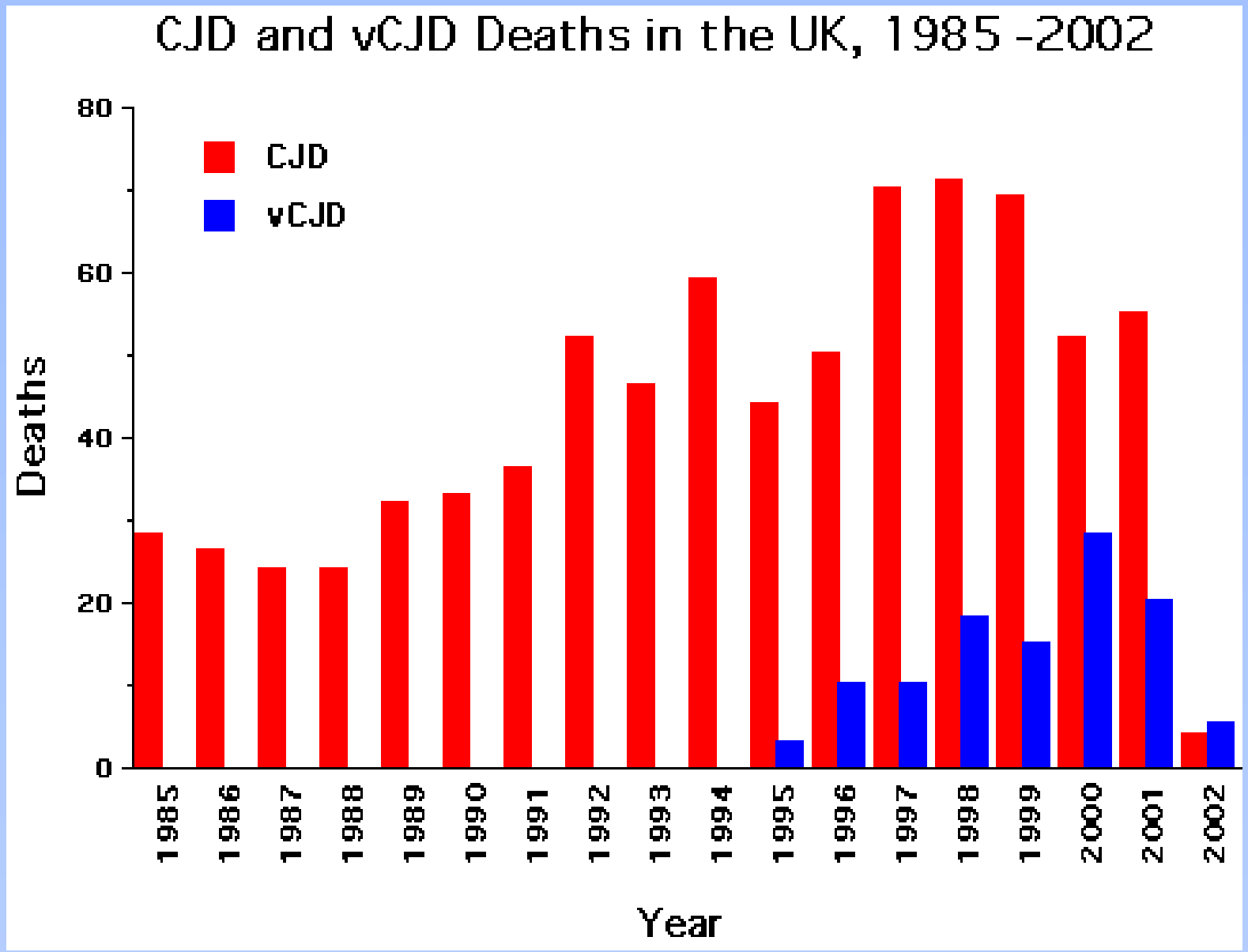
Evidence vCJD is an Infection with BSE Agent

- Unique clinical illness not seen before 1994.
- All cases ate beef products from BSE country.
- No other common risk factor was identified.
- Histopathology of vCJD resembles experimental BSE in monkeys.
- Lesion profiles in brains of mice infected with vCJD and BSE agents are unique and identical.
- BSE and vCJD agents have same incubation periods and histopathology in PrP-bovinized transgenic mice.
- BSE cows / vCJD humans have similar PrP-res “glycotypes.”

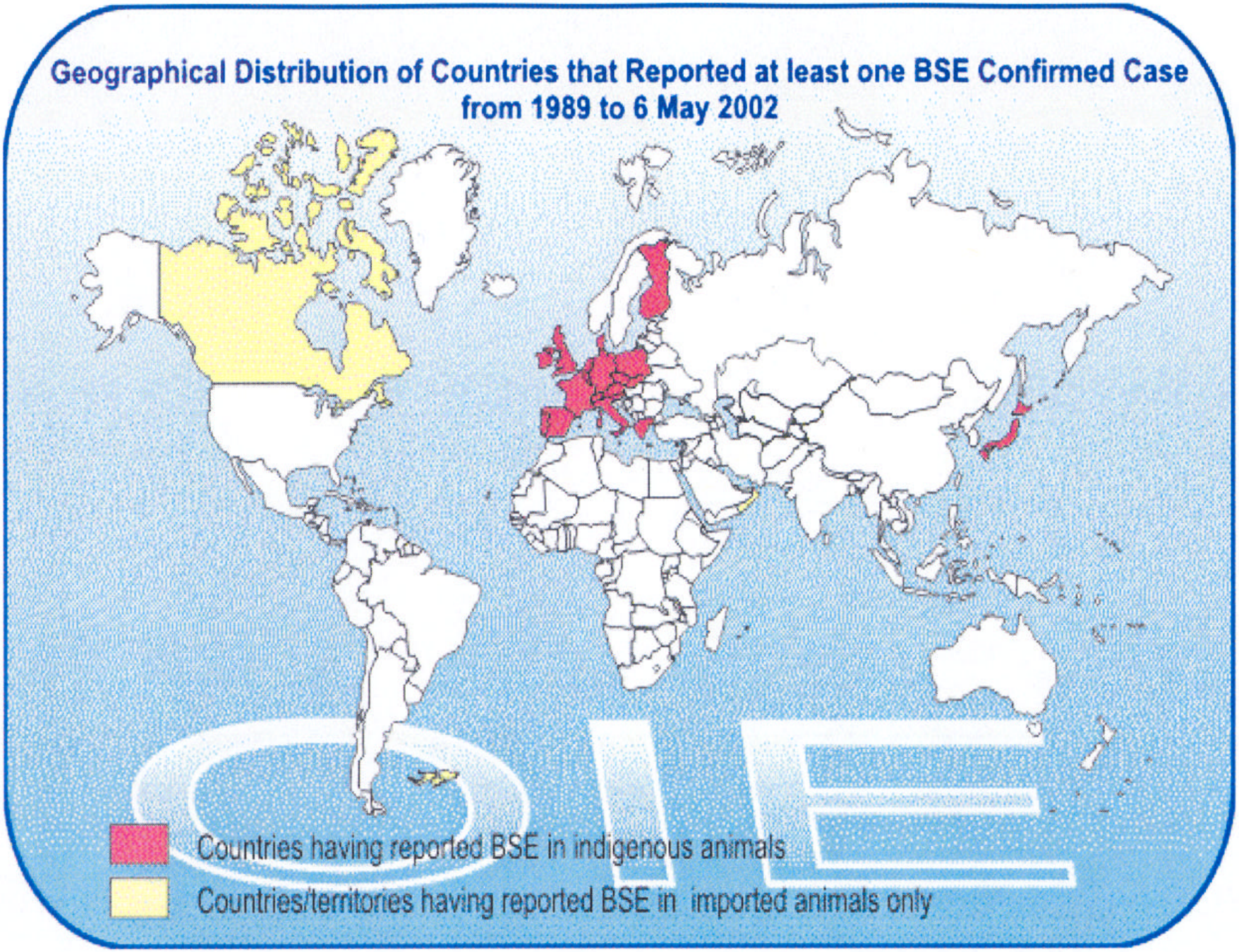
Figure2: Observed (-o-) quarterly incidence of vCJD deaths

Fitted underlying trend (___) is given with its 95% confidence limits (...)




CJD and vCJD Deaths in the UK, 1985 -2002
CJD
vCJD
Deaths
80
60
40
20
0
1985
1986
1987
1988
1989
1990
1991
1992
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
Year

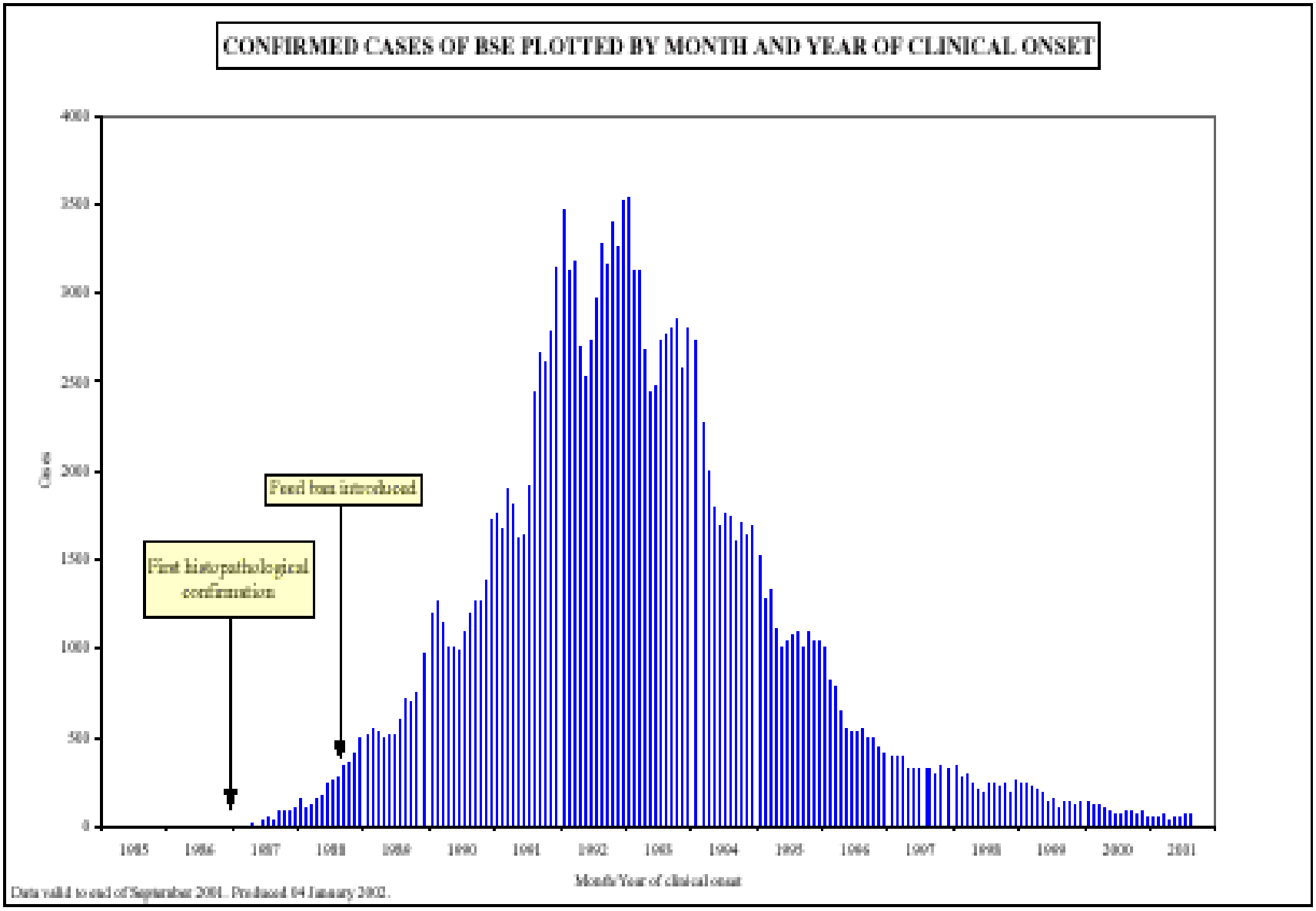
Geographical Distribution of Countries that Reported at least one BSE Confirmed Case from 1989 to 6 May 2002



22 Countries with BSE in Native Cattle

[year first reported & approx. total cases thro' Aug 2002 per OIE]

- **UK** 1986 (>182 581) [1443 in 2000; 1202 in '01; >534 in '02]
- **Ireland** 1989 (1048)
- **Switzerland** 1990 (420)
- **France** 1991 (674)
- **Portugal** 1994 (688)
- **Belgium** 1997 (86)
- **Netherlands** 1997 (41)
- **Luxembourg** 1997 (2)
- **Liechtenstein** 1998 (2)
- **Denmark** 2000 (9)
- **Germany** 2000 (210)
- **Spain** 2000 (174)
- **Italy** 2000 (54)
- **Greece** 2001 (1)
- **Czech Repub** 2001 (2)
- **Slovakia** 2001 (10)
- **Japan** 2001 (5)
- **Slovenia** 2001 (3)
- **Finland** 2001 (1)
- **Austria** 2001 (1)
- **Poland** 2002 (2)
- **Israel** 2002 (1)


CONFIRMED CASES OF BSE PLOTTED BY MONTH AND YEAR OF CLINICAL ONSET
4000
3500
3000
2500
2000
1500
1000
500
0
Cases
Feed ban introduced
First histopathological confirmation
1985
1986
1987
1988
1989
1990
1991
1992
1993
1994
1995
1996
1997
1998
1999
2000
2001
Month/Year of clinical onset
Data valid to end of September 2001. Produced 04 January 2002.

BSE Incidence per 10^6 Cows > 24 mo old

	Current	Peak	Peak Yr
Britain	258	7596	1992
Portugal	138	200	1999
Ireland	62	62	2001
Switzerland	40.6	73.6	1995
Belgium	28	28	2001
Spain	24.2	24.2	2001
Germany	20	20	2001
France	19.7	19.7	2001
Slovakia	18.3	18.3	2001
Italy	14	14	2001
Netherlands	10.3	10.3	2001
Denmark	6.8	6.8	2001
Greece	3.3	3.3	2001
Czech	2.9	2.9	2001
Finland	2.4	2.4	2001
Japan	1.4	1.4	2001
Luxembourg	0	10	1997

Precautionary Principle

European Commission COM (2000)1

(European concept—no status in US law)

- **“Where there is uncertainty as to the existence or extent of risks to human health … institutions may take protective measures without having to wait until the reality and seriousness of those risks become fully apparent.”**

  [EC Court ruling of 5 May 1998 on EC decision to ban export of UK beef.]

Approaches to Remote or Theoretical Risks of Contamination in Regulated Products

- Accept risk with disclosure, or
- Attempt to reduce risk while maintaining benefit
  - Restrict use of the product
  - Use manufacturing processes that reduce the risk
  - **Limit sources of raw materials to the safest possible**
    - » Test sources for evidence of infection
    - » **Select sources, avoiding those with history of [greatest] potential exposure to infectious agent**

History of FDA Guidances on Precautionary Measures to Reduce Possible Risk of Transmission of Creutzfeldt-Jakob Disease & Variant Creutzfeldt-Jakob Disease by Blood & Blood Products

- **Risk from human blood is theoretical only—no anecdotal or epidemiological evidence for human infection via blood; but TSE agents, including BSE agent, are found in blood of some experimentally infected animals (mice, hamsters, monkeys, sheep).**
- 1987: FDA recommended precautionary deferral of recipients of human cadaveric pituitary growth hormone as blood donors.
- 1996: FDA recommended precautionary withdrawal of blood, components, plasma derivatives from donors with CJD or at increased risk of getting CJD (iatrogenic or familial) and deferral of donors at increased risk.

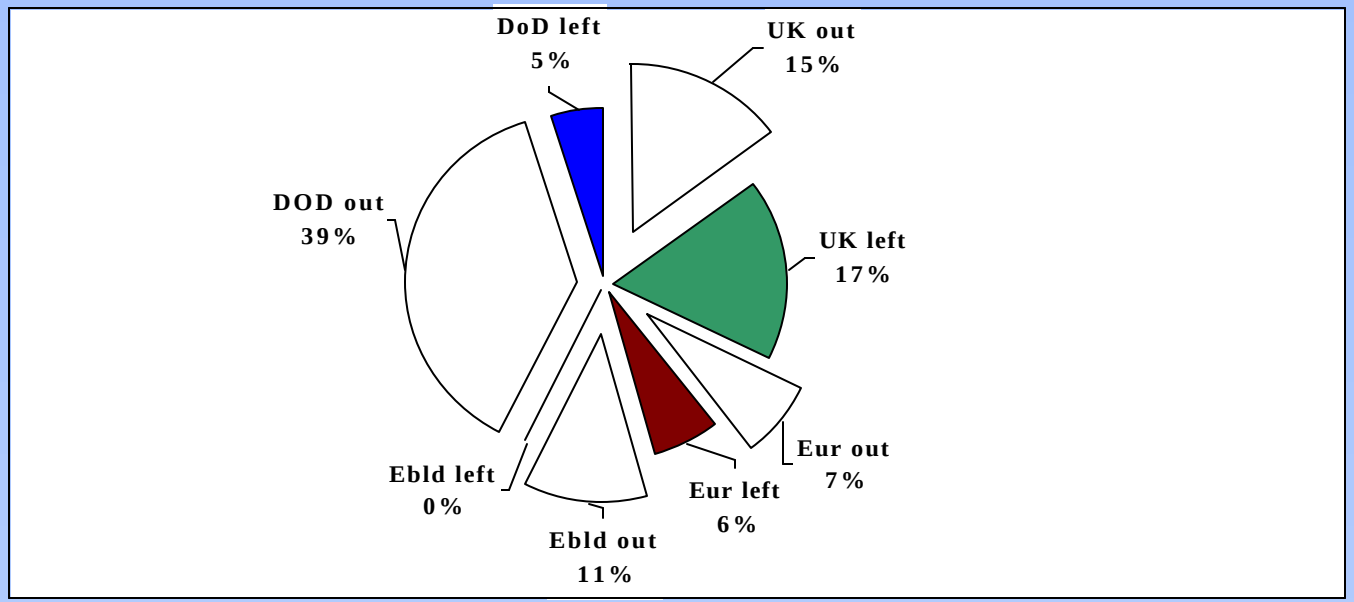
History of FDA Guidances on CJD/vCJD regarding Blood and Blood Products (continued)

- **Sept 1998, Aug 1999: FDA no longer recommended withdrawal of plasma derivatives from donors at increased risk of most forms of CJD but retained that recommendation for variant CJD (vCJD).**
  - **Additional epidemiological evidence failed to implicate blood exposure as a risk factor for sporadic CJD (sCJD).**
  - **Donors incubating sCJD cannot be detected.**
  - **CJD withdrawals contributed to shortages of plasma derivatives.**
- **But vCJD has different pathogenesis from sCJD (more abnormal PrP in lymphoid tissues), and experience with vCJD is limited.**

History of FDA Guidances on CJD/vCJD regarding Blood and Blood Products (continued)

- **Nov 1999: FDA also recommended precautionary deferral of blood donors who had spent 6 months or more in the UK between 1980 (estimated start of the BSE epidemic) and the end of 1996 (when UK had fully implemented a variety of measures to control BSE and prevent human exposure to the BSE agent).**
  - **Estimated reduction in exposure (as blood donor days spent in UK) = 87%.**
  - **Estimated expected loss of blood donors = 2.2%**

FDA Revised Guidance on CJD/vCJD & Blood Jan 9, 2002: Estimated Reduction in Risk-adjusted Donor Days after Implementation (A. Williams, OBRR, CBER, FDA)



- Estimated total risk reduction 91% (72% of current risk)
- Estimated final donor loss 4.6-5.3%
- If ARC and other programs are more aggressive, then both overall donor loss and risk reduction will be higher.

Final Guidance for Industry: Revised Precautionary Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) & Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products

January 9, 2002

www.fda.gov/cber/guidelines.htm

- **Phase I (implementation by May 31, 2002)**
  Indefinitely defer all donors who
  - **have any form of CJD or are at increased risk of CJD (no change from previous FDA guidance)**
  - **spent ≥ 3 mo in UK from Jan 1, 1980 to Dec 31, 1996**
    - **or who ever had blood transfusion in UK from 1980 to present**
    - **or who ever injected bovine insulin prepared in UK 1980 to present**
  - **spent ≥ 5 yr in France from Jan 1, 1980 to the present**
  - **spent ≥ 6 mo on US military bases from Jan 1, 1980 to end of 1990 north of Alps or end of 1996 south of Alps**

Final Guidance for Industry: Revised Precautionary Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) & Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products

January 9, 2002

www.fda.gov/cber/guidelines.htm

- **Phase II (for implementation by October 31, 2002)**
  Indefinitely defer all donors of Whole Blood but not donors of Source Plasma who spent ≥ 5 yr in Europe from Jan 1, 1980 to the present (including time in spent in UK 1980-1996 and France 1980-present)
- **Exempt from deferral are**
  - **Donors of Source Plasma who spent any period of time in Europe except UK and France**
  - **Donors of plasma/serum to manufacture CBER-approved non-injectable products (specially labeled)**

Distribution of Scrapie Infectivity Spiked into Human Blood

(Brown P et al. Transfusion 1998;38:810)

Product	Total Infectivity icLD50	% Infectivity Recovered
Whole Blood	10.0	100%
RBC	9.9	22%
WBC, platelets	8.8	7%
Plasma	8.5	3%
Plasma	8.2	100%
Cryoprecipitate	6.8	0.7%
IgG	3.9	0.006%
Albumin	2.7	0.0004%

Measures thought to be effective in protecting humans from food-borne exposures to BSE agent

- BSE control in ruminants
- Age-based slaughter schemes
- Separation of high-risk materials from edible meat
- Application of the same controls to imported and domestic meat products

Measures to protect humans from food-borne exposures to BSE agent (continued)

- **Effective control of BSE in cattle and small ruminants (sheep and goats)**
  - **OIE-compliant national surveillance programs (testing of brain tissues from animals at increased risk of BSE)**
  - **Prohibitions on feeding most mammalian proteins to ruminants ("feed bans") and steps to prevent accidental feeding of prohibited proteins**
  - **Prompt condemnation and destruction of animals with signs of BSE**
  - **Preventive culling of animals at increased risk**
  - **Adequate compensation to owners (encourages compliance)**

Measures to protect humans from food-borne exposures to BSE agent (continued)

- **Age-based slaughter schemes**

  Intended to reduce risk by prohibiting consumption of meat products from ruminants slaughtered after an age when substantial amounts of BSE agent are likely to be present in tissues, generally taken to be no later than 24 to 30 months for cattle

  Example: UK "Over-Thirty-Month" Rule

Measures to protect humans from food-borne exposures to BSE agent (continued)

- **Separation of high-risk materials from edible meat products**
  - **Prohibition of slaughter methods that may embolize brain tissue, possibly contaminating meat, e.g. intracranial air injection and "pithing"**
  - **Removal of "specified risk materials" (SRM=CNS, lymphoid, intestinal tissues) from ruminant carcasses at the time of slaughter and effective segregation of SRM from edible materials**
  - **Prohibition of "advanced" or "mechanical" meat recovery systems (may contaminate meat with ganglia, spinal cord, possibly brain)**

Measures to protect humans from food-borne exposures to BSE agent (continued)

- **Application of same measures to protect the human food chain to imported food and domestically produced food**

Infectivity of Neural Tissues from Humans with TSEs

(Brown P et al. Ann Neurol 1994;35:513-529)

Tissue or Fluid Tested	Positive/ Total Tested	% Positive
Brain	234/259	90
Eye*	4/5	80
Spinal cord	4/6	67
CSF	3/26	12

* Retina, vitreous, lens, cornea

Distribution of Infectivity in Tissues of Patients with Spongiform Encephalopathy

(Brown P et al. Ann Neurol 1994;35:513-529)

Tissue	Transmitted/Inoculated
Lung	50% (2/4)
Lymph node	20% (3/15)
Kidney	18% (5/28)
Liver	11% (4/35)
Spleen	10% (3/31)

Update on TSEs: Recent Laboratory Research Results

- Abnormal prion protein PrP^{Sc} detected in TSE urine (not infectious; not confirmed for Dx use)
- Abnormal prion protein detected in scrapie mouse muscle (infectious; not yet found in other TSEs)
- EDRF mRNA reduced in animal TSEs (not confirmed in humans with CJD)
- Infectivity eliminated from cell cultures by quinacrine, chlorpromazine, antibodies (IND clinical trials started)
- Improved TSE Dx (PrP^{Sc} ↑sensitivity; PrP-Tg mice for infectivity detection: research use only)
- Blood of sheep with BSE (& scrapie) infects other sheep.

Update on TSEs: Recent Important Events

- No CJD in 22 UK recipients of blood products from donors who later got vCJD—limited observations
- BSE recognized in cattle of several more countries (additional BSE countries suspected)
- Variant CJD affected 1 person in USA and 1 in Canada (former UK residents).
- Chronic wasting disease of deer and elk is found west of Rocky Mountains in CO and 2 new states (NB, WI) in addition to original focus (CO, WY).
- FDA continues trying to maintain consistent rational TSE policies.

Expression of PrP^C on Blood Cells of Various Mammalian Species (J. Vostal & al.)

Species	Platelets	RBCs	Lymph	Mono	Gran
Human 10	++	+	+++	+++	±
Chimp 1	++	not done	++	+++	±
Cat 3	++	–	++	++	±
Cow 3	±	–	+++	+	–
Sheep 5	±	–	++	+	–
Hamst 10	–	–	–	–	–
Mouse 10	–	+	±	±	±

PrP^C on Blood Cells: ? Relevance of Animal Models (J. Vostal & al)

- **Expression of PrP^C on blood cells of various animal species used in TSE infectivity studies is different from that in humans.**
- **Rodents may not be appropriate animal models to study TSE infectivity in blood.**

Scrapie Agent Decontamination Test
(263K-scrapie-infected hamster brain dried on glass survived autoclaving.)

Autoclaving Regimen	Control Scrapie $\log_{10}$ LD_{50}	Objects Infected (% of 10)	Animals Infected (% of 40)
121° C x 60'	>4	**100%**	**100%**
132° C x 60'	~7	**90%**	**57%**
134° C x 60'	~7	**100%***	**75%***

* Two objects were assayed in eight hamsters. Mean survival was 228 da ± 85 da. Brains of all dying hamsters contained PrP-res.

Participants in CBER TSE Activities (partial list)

- **OBE**
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- **OBRR**
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  - Ruth Solomon & al (tissue staff)
  - Jaro Vostal & al (DH)
  - Alan Williams (DBA)
  - Pat McMahon
  - Olga Maximova
  - Kitty Pomeroy
  - Rolf Taffs (Jeanette Ridge)
- **OCBQ**
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- **OD**
  - Bill Freas
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- **OTRR**
  - Jerry Feldman
- **OVRR**
  - Chris Anderson & al
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